REMARKS

Formal Matters

Applicants note that the rejection of claims 1 and 4 under 35 U.S.C. § 112, second paragraph, as being indefinite was not maintained in the present Office Action and is therefore deemed withdrawn.

Claims 1, 4-11, and 23-27 are pending in this application.

Enablement Rejection

Claims 1, 4-11, and 23-25 were rejected by the Office because the specification allegedly does not reasonably provide enablement to make or use the present invention. *See* Office Action at page 2. The Office generally alleges that the specification is not enabling because the specification does not teach (1) a PTHrP antibody that binds to a portion of PTHrP other than the N-terminal 1-34, (2) how to make a "modified form" of a PTHrP antibody, and (3) which particular anti-PTHrP antibody maintains vasopressin level and which increases vasopressin level. *See* Office Action at pages 2-6. Specifically the Office states that the "specification does not teach how to make 'modified form' of antibody that bind to *all* 'PTHrP', much less which particular anti-PTHrP antibody maintains vasopressin level and which particular anti-PTHrP antibody increases vasopressin level in vivo." Office Action at page 3 (emphasis in original). Applicants respectfully traverse.

The test for enablement is "whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." M.P.E.P. § 2164.01.

Contrary to the Office's arguments, the test for enablement is not whether Applicants have actually reduced to practice all embodiments of the invention. For instance, the Office asserts that only antibodies against the N-terminal 1-34 amino acids are enabled. Applicants did, in fact, actually reduce to practice an anti-PTHrP antibody directed to the 1-34 fragment of PTHrP. *See* specification, "Reference Example 1: Preparation of hybridomas producing anti-PTHrP (1-34) mouse monoclonal antibody," pages 23-24. However, the disclosure generally describes how to produce antibodies directed to any portion of PTHrP, using the entire protein as a sensitizing antigen. *See* specification, pages 5-8. The specification specifically states that "the purified PTHrP protein is used as a sensitizing antigen. Alternatively, a 34-amino acid peptide of the N-terminal region of the PTHrP may be chemically synthesized as the sensitizing antigen." Specification, page 5, lines 26-28. Thus, one of ordinary skill in the art would be able to make and use an antibody directed to any epitope of the PTHrP antigen. Applicants should not be limited to the antibody directed to the N-terminal portion of PTHrP actually reduced to practice.

The Office also alleges that one of ordinary skill in the art would not be able to make or use a "modified form" of a PTHrP antibody. Applicants respectfully disagree. The specification at pages 13-14 states:

> As a modified form of the above-mentioned antibodies, for example, anti-PTHrP antibody conjugated to any molecule (e.g., polyethylene glycol; PEG) may also be used. Such modified antibodies are also encompassed in the "antibody" of the present invention. The modified antibodies can be prepared by chemical modifications of the antibodies. The

> chemical modification techniques suitable for this purpose have already been established in the art.

Chemical modifications of antibodies and the conjugation of antibodies to other molecules, such as PEG, were well known to those of skill in the art at the time the application was filed. In light of this specific disclosure and the disclosure of methods of making and using PTHrP antibodies of the invention generally, one of ordinary skill in the art would be able to make and use "modified forms" of PTHrP antibodies.

The Office also requires identification of which PTHrP antibodies maintain vasopressin level and which increase vasopressin level. Again, this requirement is not part of the enablement test outlined above. The disclosure contains sufficient information by which one of ordinary skill in the art can test to determine if a particular PTHrP antibody maintains or increases vasopressin level. Even if inoperative embodiments exist, the binding and neutralizing activity of the antibody can be easily tested to select the antibodies that maintain or increase vasopressin levels. *See* specification at page 16. Furthermore, the specification teaches the use of a tumor-transplanted animal model to determine if a particular antibody maintains or increases vasopressin level *in vivo*. *See* specification at pages 19-23. No undue experimentation is required by one of ordinary skill in the art to select an antibody that maintains or increases vasopressin levels. In light of the arguments above, Applicants respectfully submit that claims 1, 4-11, and 23-25 are enabled and request that the Office withdraw this rejection.

Written Description Rejection

Claims 1, 4-11, and 23-25 have been rejected by the Office under 35 U.S.C. § 112 as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention." Office Action at page 6. Specifically, the Office alleges that the specification does not provide written description for "any antibody such as any monoclonal, humanized, chimeric, antibody fragment and any 'modified form' of said fragment that binds to *all* 'PTHrP' and *any* part of PTHrP other than N-terminal 1-34 of human PTHrP for a method of *maintaining* or *increasing* low vasopressin level." Office Action at page 6 (emphasis in original). Applicants respectfully traverse.

Contrary to the Office's assertion, the written description requirement does not necessitate "written description about the structure of the CDRs of all antibodies that correlate with function." *See* Office Action at page 6. Furthermore, the claims should not fail the written description requirement because "there is insufficient written description about which amino acids within the binding fragment of any antibody to be modified by substitution, deletion, addition and/or combination thereof such that the 'modified binding fragment' still maintains its binding specificity." Office Action at page 7.

The Office is again improperly attempting to limit the scope of the claims based on an actual reduction to practice disclosed in the specification. The Office's position is

inconsistent with the Office's own Synopsis of Application of Written Description Guidelines, which indicates that written description can be met by

> [s]how[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

Guidelines, 66 Fed. Reg. at 1106 (emphasis added). In *Noelle v. Lederman*, 355 F.3d at 1349, the court, basing its reasoning on past precedent, stated that "as long as an applicant has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen."

Applicants respectfully submit that the structure of full-length PTHrP is disclosed in the specification at, for instance, page 5, lines 19-21, in the Suva *et al.* reference. Based on the Office's own guidelines and the holdings of the courts, Applicants assert that the claims fulfill the written description requirement and request that the Office withdraw this rejection.

Indefiniteness Rejection

Claims 1, 4-8, and 23-27 have been rejected by the Office under 35 U.S.C. § 112, second paragraph as being indefinite because they fail to point out and distinctly claim the subject matter defined as the invention. *See* Office Action at page 9. Specifically, the Office rejected claims 1, 26, and 27 because the term "maintaining the

level of vasopressin" is not the same as "increasing" the low level of vasopressin level since it appears to be mutually exclusive. *Id.* Further, the Office states that it is not clear which anti-PTHrP would result in increasing vasopressin level and which would result in maintaining the level of vasopressin. *Id.* Applicants respectfully traverse. Section 2173.05(b) of the M.P.E.P. states that "[a]cceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification." One of ordinary skill in the art would understand that administration of the at least one PTHrP antibody would either "maintain" or "increase" vasopressin level. The terms "maintain" and "increase" have their normal meaning and would be interpreted as mutually exclusive, as the Office has also understood, especially in light of Applicants use of the conjunction "or." The Office has not given any reasoning why the mutually exclusive use of "maintaining" or "increasing" low vasopressin level would not be clear to one of ordinary skill in the art; either one or the other will occur. Applicants note that the action of a particular antibody may also depend on the context, *e.g.*, an antibody may maintain vasopressin in patient X and increase vasopressin level in patient Y.

Furthermore, the administration of more than one PTHrP antibody does not render the claims indefinite. One of ordinary skill in the art would understand that the aggregate effect of administration of the at least one PTHrP antibody results in maintaining or increasing vasopressin level. It is not necessary to attribute either "maintaining" or "increasing" to each antibody administered. As Applicants noted above, the action of a particular antibody may depend upon the context. Applicants

respectfully assert that the phrase "maintaining or increasing low vasopressin level" is clearly understood by one of ordinary skill in the art and request that the rejection of claims 1, 26, and 27 be withdrawn.

The Office rejected claims 1, 26, and 27, because the term "at least one" suggests that "there is another anti-PTHrP" antibody. *Id.* Applicants respectfully traverse. The standard for indefiniteness, as described above, involves the clarity of the claims and whether one of ordinary skill in the art would understand the claims in light of the specification. One of skill in the art would understand, as the Office did, that more than one type of PTHrP antibody of the invention may be administered to a patient. For instance, the types of PTHrP antibodies encompassed by the invention include, but are not limited to, humanized, chimeric, or monoclonal antibodies. *See, e.g.,* specification, page 2, lines 24-25. Applicants respectfully submit that one of skill in the art would understand that the administration of one or more PTHrP antibodies is claimed in light of the specification. The Office's argument that the term "at least one" suggests that there is more than one antibody, as it should, is not a sufficient ground for an indefiniteness rejection. The Office has not described why the term "at least one" makes the scope of the claimed subject matter unclear. Applicants therefore respectfully request that the indefiniteness rejection of claims 1, 4-8, and 23-27 be withdrawn.

Anticipation Rejection

The Office rejected claims 1, 5-11, and 26-27 under 35 U.S.C. § 102(e), as being anticipated by U.S. Patent No. 6,903,194 ('194 patent). *See* Office Action at page 10.

The Office states that the '194 patent teaches a method of treating at least one symptom in a patient with cancer that inherently caused low vasopressin level (see col. 60, lines 6-18) by administering to the patient at least one anti-PTHrP antibody. *Id.* Further, the Office states that the "reference method inherently maintains or increases the level of vasopressin levels because the reference antibody used by the reference methods is the same antibody in the claimed method." *Id.* Applicants respectfully traverse.

As section 2131 of the M.P.E.P. states, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." The '194 patent does not expressly mention vasopressin level or the effect of an anti-PTHrP antibody on vasopressin level. The Office's particular citation to the '194 patent at col. 60, lines 6-18 does not even mention vasopressin.

Applicants also respectfully submit that the '194 patent does not inherently teach methods of maintaining or increasing vasopressin levels, as the Office suggests. The M.P.E.P. provides that "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." M.P.E.P. § 2112, IV, citing *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). Furthermore, Applicants respectfully note that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given

set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745 (Fed Cir. 1999) (emphasis added). There is nothing in the record that demonstrates that any of the hypercalcemia patients discussed in the '194 patent were suffering from low vasopressin levels. The Office does not provide a basis in fact and/or technical reasoning to support their statement that the hypercalcemia "inherently caused low vasopressin level." Without such support it is impossible to state that administration of a PTHrP antibody necessarily maintained or increased the low vasopressin levels. The unlikely and purely coincidental possibility that some patients may be suffering from both hypercalcemia and low vasopressin level and both conditions may be treated by administration of a PTHrP antibody does not legally suffice to show anticipation. Therefore, Applicants request that the Office withdraw this anticipation rejection of claims 1, 5-11, and 26-27.

Obviousness Rejections

The Office rejected claims 1, 4, and 25 as being unpatentable over U.S. Patent No. 6,903,194 in view of *Harlow* or U.S. Patent No. 4,946,778. *See* Office Action at page 11. The Office also rejected claims 23-24 as being unpatentable over U.S. Patent No. 6,903,194 in view of *Harlow*, as applied to *Kitamura*. *See* Office Action at page 12. Applicants respectfully traverse.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) all claim limitations must be taught or suggested, (2) there must be some suggestion or motivation to modify the references or combine reference teachings, and (3) there must be a reasonable expectation of success. M.P.E.P. § 2143.03.

Applicants respectfully submit that the references provided by the Office do not teach or suggest all claim limitations. Specifically, the '194 patent, *Harlow*, the '778 patent, and *Kitamura* do not teach or suggest "maintaining or increasing vasopressin levels," as the pending claims require.

As discussed above, the '194 patent does not expressly mention vasopressin or, for that matter, any effect of an anti-PTHrP antibody on vasopressin level. The Office's particular citation to the '194 patent at col. 60, lines 6-18 does not even mention vasopressin. Further, the '194 patent does not suggest that the administration of PTHrP antibodies is able to maintain or increase vasopressin level. *Harlow*, which teaches a method of producing an antibody fragment, and the '778 patent, which teaches a method of producing single chain antibodies, do not cure the defects of the '194 patent. *Kitamura*, which teaches a PEG-conjugated antibody fragment, also does not cure these defects. In fact, none of the references cited by the Office teach or suggest maintaining or increasing vasopressin levels, which the claims require. Applicants therefore respectfully submit that all claim limitations are not taught or suggested by the cited references. Therefore, the Office has not established a *prima facie* case of obviousness and the rejection of claims 1, 4, and 25 and the rejection of claims 23-25 should be withdrawn.

The Office rejected claims 1, 4, 7-11, and 25 as being obvious over *Yamamoto*, in view of *Sato*, *Harlow*, and *Hotta*. *See* Office Action at page 13. The Office also rejected claim 5 as obvious over *Yamamoto*, in view of *Sato*, *Harlow*, and *Hotta*, and further in view of U.S. Patent No. 6,180,370. *See* Office Action at page 17. Applicants

respectfully traverse. Specifically, the Office has not demonstrated (1) a reasonable expectation of success or (2) motivation to modify the references or combine reference teachings, as required by the criteria set forth in M.P.E.P. § 2143.03 to establish a *prima facie* case of obviousness.

Sato describes a PTHrP antibody, but it does not teach that administration of a PTHrP antibody "maintains or increases vasopressin level." *Yamamoto* does not teach PTHrP antibodies, but teaches that a fragment of PTHrP stimulates release of arginine-vasopressin. There is no suggestion or motivation, as the Office alleges, to substitute the PTHrP fragment taught by *Yamamoto* with the PTHrP antibody taught by *Sato*. *Sato* states that the anti-PTHrP antibodies described in the paper "were found to eliminate the biologic activity of PTHrP (1-34)." *Sato*, page 850, left column, second paragraph (emphasis added). Yet, *Yamamoto* concludes that "PTHrP (1-34), but not PTH (1-34), causes the release of AVP." *Yamamoto*, abstract, page 2066, last sentence (emphasis added). Therefore, the modification proposed by the Office, substituting the fragment of *Yamamoto* with the antibody of *Sato*, would render the invention unsatisfactory for its intended purpose. Elimination of the biologic activity of PTHrP (1-34) with the antibody of *Sato*, would eliminate the arginine-vasopressin release taught in *Yamamoto*. Section 2143.01 of the M.P.E.P. states that "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." (*citing In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984)). Therefore,

Applicants respectfully submit that the Office has not demonstrated a prima facie case of obviousness.

Even assuming there is a suggestion or motivation to make the proposed modification, *Yamamoto* does not provide a reasonable expectation of success. *Yamamoto* demonstrated that administration of PTHrP(1-34) resulted in an increase of arginine-vasopressin levels. Yet, administration of PTHrP(7-34) or PTH(1-34), a similar protein, had no significant effect on arginine-vasopressin levels. Thus, even if the fragment of *Yamamoto* was substituted with the antibody of *Sato*, there is no reasonable expectation of success that the antibody would have an effect on arginine-vasopressin levels. Given that PTHrP(7-34) and PTH(1-34) did not affect arginine-vasopressin levels, it would not be obvious to one skilled in the art that antibodies against PTHrP would increase vasopressin levels. Therefore, the teachings of *Yamamoto* and *Sato* do not provide one skilled in the art with a reasonable expectation of success.

Neither *Harlow*, *Hotta, or the* '370 patent cure the defects of *Yamamoto* in view of *Sato*. *Harlow* teaches a method of producing an antibody fragment, the '370 patent teaches a method of producing chimeric antibodies and humanized antibodies, and *Hotta* describes a case study of hypercalcemia in an euthryoid patient. However, none of the references teach or suggest anti-PTHrP antibodies or increasing vasopressin levels in patients. Therefore, Applicants respectfully request that the Office withdraw the obviousness rejection of claims 1, 4, 7-11, and 25 and the obviousness rejection of claim 5.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: February 23, 2006

By: Rebecca M. McNeill
for: Amy E. Purcell Reg. No. 43,796
Reg. No. 53,492